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(54) Title: STERILIZATION OF SILICONE PREPARATIONS

(57) Abstract: Disclosed herein is a method for producing sterile silicone preparations which comprises sterilizing a silicone raw material, prior to curing, by the high-pressure steam sterilization method.

DESCRIPTION

STERILIZATION OF SILICONE PREPARATIONS

TECHNICAL FIELD

This invention relates to a process for sterilizing a silicone raw material for producing silicone preparations.

BACKGROUND ART

A preparation to be administered to a living body directly, e.g., intravenously, subcutaneously, intramuscularly or topically, is preferably administered in a sterilized, sterile state in view of safety reasons. Most of such preparations are solutions, which can be sterilized by filtering. Drug delivery systems being recently under development, on the other hand, have provided some solid preparations to be administered subcutaneously, intramuscularly, or topically into a living body. Methods for the sterilization of such solid preparations include a dry-heat sterilization, high-pressure steam sterilization, gaseous ethylene oxide sterilization, radiation irradiation, all of which are general sterilization methods for a solid product. Several silicone preparations have been developed recently for use in implanting in a living body, and such preparations have been treated with a gaseous ethylene oxide sterilization to achieve sterilization. However, gaseous ethylene oxide is much chemically reactive and is associated with problems such that it may react with an active ingredient. Dry heat sterilization and high-pressure steam sterilization are hardly applicable

to silicone preparations containing an active ingredient that is unstable to heat or is susceptible to steam. Further, radiation sterilization is so large in radiation energy that a substance sterilized by this method may be denaturated although it can be carried out at room temperature. According, this method has not been used widely as a sterilization for preparations containing an active ingredient. Under the circumstances, in order to produce sterile silicone preparations containing an active ingredient, of which the stability and properties may be widely varied, it is necessary to sterilize the active ingredient and silicone raw material separately, prior to mixing and curing.

Silicone raw material for producing silicone preparations is composed of Component group I that contains organopolysiloxane as a primary agent, a filler, a curing catalyzer etc., and Component group II that contains organopolysiloxane as a primary agent, a filler, a crosslinking agent, etc. By mixing these two Components, the curing reaction is proceeded to give an elastomer. Both Components cannot be sterile-filtrated as they are either highly viscous liquid or in a slime-like state. Silicone raw material has not been investigated for a sterilizing method therefor and its thermal stability. The present inventors investigated to find that the silicone raw material deteriorates when exposed to high temperature for a long time, thus loosing its utility. Further, any method for sterilizing up to the deep inner part of such silicone raw material that is very viscous highly liquids or in slime state has been also unknown.

DISCLOSURE OF THE INVENTION

The present invention provides a process for sterilizing a silicone raw material up to the inner part without inducing deterioration of the silicone raw material for producing a silicone preparation containing an unstable active ingredient.

As a result of extensive studies to attain the aim as above, the present inventors found that silicone preparations can be prepared by sterilizing a silicone raw material for producing the preparation using a high-pressure steam sterilization to give a sterile silicone raw material, followed by mixing it with an active ingredient, additives, or the like each of which has been separately sterilized, and curing the mixture. On the basis of the findings, the inventors have accomplished the present inventions.

The present invention relates to:

(1) A process for sterilizing a silicone raw material for producing a silicone preparation, which comprises a step of conducting a high-pressure steam sterilization on the silicone raw material prior to curing;

(2) The process according to (1), wherein the sterilization is conducted at a temperature ranging from about 115°C to about 135°C in a high-pressure steam sterilization apparatus;

(3) The process according to (1) or (2), wherein the sterilization is conducted for from about 30 minutes to about 24 hours in a high-pressure steam sterilization apparatus;

(4) The process according to (1), (2) or (3), in which the sterilization is conducted by generating or introducing saturated steam vapor into a high-pressure steam sterilization apparatus;

(5) The process according to (1), (2), (3) or (4), in which the pressure in a high-pressure steam sterilization apparatus is from about 0.7 to about 2.2 kgf/cm^2;

(6) The process according to (1), (2), (3), (4) or (5), in which the sterilization is conducted on a silicone raw material having a thickness of about 10 mm or less;

(7) The process according to (6), in which the silicone raw material is in a sheet form;

(8) The process according to (1), (2), (3), (4), (5), (6) or (7), in which the silicone raw material is of an addition-polymerizable type by catalytic action of a platinum compound;

(9) A silicone raw material sterilized by the process according to (1), (2), (3), (4), (5), (6) or (7);

(10) A silicone preparation containing an active ingredient, which preparation is produced from a silicone raw material sterilized by the process according to (1), (2), (3), (4), (5), (6) or (7);

(11) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping a silicone raw material into a sheet form, and

b. a step of sterilizing the sheet in a high-pressure steam sterilization apparatus;

(12) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping a silicone raw material into a sheet form, and

b. a step of putting the silicone raw material of a sheet form in a sterilizing bag,

c. a step of sterilizing it in a high-pressure steam sterilization apparatus;

(13) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping a silicone raw material into a sheet form having a thickness of about 10 mm or less,

b. a step of putting the silicone raw material of a sheet form in a sterilizing bag,

c. a step of sterilizing it in a high-pressure steam sterilization apparatus;

(14) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting the silicone raw material of a sheet form in a sterilizing bag,

c. a step of sterilizing it in a high-pressure steam sterilization apparatus;

(15) The process according to (11), (12), (13) or (14) in which the sterilization is conducted at a temperature ranging from about 115° C to about 135°C in a high-pressure steam sterilization apparatus;

(16) The process according to (11), (12), (13), (14) or (15) in which the sterilization is conducted for from about 30 minutes to about 24 hr. in a high-pressure steam sterilization apparatus;

(17) The process according to (11), (12), (13), (14), (15) or (16) in which a saturated steam is generated or introduced into a high-

pressure steam sterilization apparatus;

(18) The process according to (11), (12), (13), (14), (15), (16) or (17) in which the pressure in a high-pressure steam sterilization apparatus is from about 0.7 to about 2.2 kgf/cm^2;

(19) The process according to (11), (12), (13), (14), (15), (16) or (17), which further comprises a step of using a biological indicator for confirming sterilization.

(20) The method according to (19), wherein the biological indicator is *Bacillus Stearothemophilus.*

(21) The process according to (19) or (20), wherein the amount of the biological indicator is 10^6.

(22) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 10 mm or less,

b. a step of putting the silicone raw material of a sheet form in a sterilizing bag,

c. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus.

(23) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting a biological indicator on the center of said sheet, followed by folding said sheet at a thickness of about 10 mm or less,

c. a step of putting the folded sheet in a sterilizing bag,

d. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus.

(24) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting a biological indicator of 10^6 on the center of said sheet, followed by folding said sheet at a thickness of about 10 mm or less,

c. a step of putting the folded sheet in a sterilizing bag,

d. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus.

(25) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting *Bacillus Stearothermophilus* as a biological indicator

on the center of said sheet, followed by folding said sheet at a thickness of about 10 mm or less,

c. a step of putting the folded sheet in a sterilizing bag,

d. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus.

(26) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting *Bacillus Stearothermophilus* of 10^6 as a biological indicator on the center of said sheet, followed by folding said sheet at a thickness of about 10 mm or less,

c. a step of putting the folded sheet in a sterilizing bag,

d. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus.

(27) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting *Bacillus Stearothermophilus* of 10^6 as a biological

indicator on the center of said sheet, followed by folding said sheet at a thickness of about 10 mm or less,

c. a step of putting the folded sheet in a sterilizing bag,

d. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus,

e. a step of confirming the sterilization by culturing the biological indicator in a culture medium.

(28) A process for sterilizing a silicone raw material by a high-pressure steam sterilization method, which comprises:

a. a step of shaping the silicone raw material into a sheet form having a thickness of about 5 mm or less,

b. a step of putting *Bacillus Stearothermophilus* of 10^6 as a biological indicator on the center of said sheet, followed by folding said sheet at a thickness of about 10 mm or less,

c. a step of putting the folded sheet in a sterilizing bag,

d. a step of sterilizing at a temperature ranging from about 115 °C to about 135 °C for from about 30 minutes to about 24 hours by generating or introducing a saturated steam at a pressure of from about 0.7 to about 2.2 kgf/cm^2 in a high-pressure steam sterilization apparatus,

e. a step of confirming the sterilization by culturing the biological indicator in a casein digestive culture medium at a temperature ranging from 55 °C to 60 °C for 7 days.

Silicone raw material is not limited to a particular species as long as it forms a gummy substance by curing, and preferably it is of an addition-polymerizable type caused by catalytic action of a platinum compound. More preferably, it is a millable type or a two component LTV (Low Temperature Vulcanizing), and, most preferably, it is SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, or Dow Corning (registered trade mark) MDX-4-4210 medical grade elastomer, or the like.

Active ingredients include, but are not limited to, a low molecular weight compound, a peptide, a protein, a glycoprotein, a polysaccharide, a toxoid useful as a vaccine, an antigen, an antibody, a gene, a virus, or the like.

Some specific examples of low molecular weight compounds include, but not limited to, antibiotics such as avermectin, ivermectin, spiramycin, ceftiofur, mero- penem, phosphomycin; antibacterial such as amoxicillin, erythromycin, oxy- tetracyclin, lincomycin; antiinflammatory agents such as dexametazone, phenyl- butazone; hormones such as levothyroxine; adrenocortical steroids such as dexametazone palmitate, triamcinolone acetonide, halopredone acetate; nonsteroidal antiinflammatory agents such as indometacin, aspirin; arterial occlusion drugs such as prostaglandin E1; anticancer agents such as actinomycin, daunomycin, bleomycin, mitomycin, fluorouracil, peplomycin, hydroxyurea, neocarzinostatin, sizofiran, estra- mustine, carboplatin; antidiabetics such as acetohexamide; and bone disease drugs such as estradiol.

Some specific examples of peptides, proteins, glycoproteins, or

polysaccharides include, but not limited to, cytokines such as an interferon, an interleukin; hematopoietic factors such as a colony stimulating factor, an erythropoietin; hormones such as a growth hormone, a growth hormone releasing factor, a calcitonin, a lutenizing hormone, a lutenizing hormone releasing hormone, an insulin; growth factors such as a somatomedin, a nerve growth factor, a neurotrophic factor, a fibroblast growth factor, a hepatocyte growth factor; a cell adhesive factor; an immunosuppressive agent; enzymes such as an asparaginase, a superoxide dismutase, a tissue plasminogen activating factor, an urokinase, a prourokinase; a bone metabolism related proteins such as BMP (Bone Morphogenetic Protein); antigens; antibodies; and the like.

The active ingredient includes not only those exhibiting therapeutic effect by themselves, but also those showing physiological activity or those assisting or inducing physiological activity. Such active ingredients include, for example, adjuvants used in vaccine as typified by saponin. In this case, a vaccine may be comprised in the preparation so as to prepare a sustained-release formulation containing the vaccine.

Active ingredient can be used solely or together with other several active ingredients depending on the disease or route of administration.

An additive can be comprised if required for the purpose of stabilizing an active ingredient or of controlling the release of an active ingredient. The additive shall be pharmaceutically acceptable and include, but not limited to, a salt such as sodium chloride, sodium

citrate; an amino acid such as glycine, alanin, sodium glutamate; a carbohydrate such as lactose, mannitol; a protein such as gelatin, collagen, albumin; a synthetic polymer such as polyethylene glycol; and a surface active agent such as sodium laurylsulfate, sodium deoxycholate. One or more of the additives can be used, if necessary.

The process and the silicone raw material of the present invention are applicable for producing any preparation having various shape, construction, or composition. Such preparations include those as disclosed in Japanese Patent Nos. 2033056 and 2056085; and Japanese Patent application Nos. 331467/1993, 256170/1998, 148591/1998, 155343/1998 and 319108/1999.

BEST MODE FOR CARRYING OUT THE INVENTION

The following illustrates the processes for producing sterilized silicone preparations according to the process of the present invention.

Step 1: Sterilization

Silicone raw material can be shaped in any form that allows infiltration of steam required for sterilization into the inner part. It may preferably be processed to give a shape in which the distance from the surface exposed to external environment through the deepest part is 5 mm or less, and more preferably the distance is 2.5 mm or less. For example, the silicone raw material is processed to give a sheet form using a roll or press machine. The thickness of the sheet is not limited as far as it allows infiltration of a steam into the inner part necessary for sterilization. It is preferably 10 mm or less, more preferably 5 mm

or less. Alternatively, when the silicone raw material is in a block form, an insection can be made at an appropriate spacing to form a path for passing the steam. The appropriate spacing is not limited as far as it allows infiltration of the steam necessary for sterilization into all part of the block. It is preferably 10 mm or less, more preferably 5 mm or less. The silicone raw material thus processed is packaged in a sterilizing bag, sealed it, and the bag is placed in a high-pressure steam sterilization apparatus. The sterilizing bag refers to a packing material for sterilization that is used for the purpose of blocking penetration of microorganisms to keep a sterile condition after sterilization, and includes for example those made of paper or paper film for a high-pressure steam sterilization. Temperature for sterilization is an appropriate temperature ranging from about 115 to about 135°C, preferably from about 120 - about 125°C, and more preferably about 121°C. When the sterilization is conducted at an appropriate temperature ranging from about 115 to about 135°C, the pressure in a high-pressure steam sterilization apparatus can be from about 0.7 to about 2.2 kgf/cm^2. Retention time after reaching a sterilizing temperature is set depending on the temperature, the thickness of silicone raw material, or the spacing of insection. At about 115°C, for example, it is preferably from about 30 minutes to about 24 hours, more preferably from about 30 minutes to about 12 hours, most preferably from about 30 minutes to about four hours. At about 121° C, for example, it is preferably from about 15 minutes to about 12 hours, more preferably from about 15 minutes to about eight hours, most preferably from about 15 minutes to about four hours. At about

135°C, for example, it is preferably from about three minutes to about three hours, more preferably from about three minutes to about two hours, most preferably from about three minutes to about one hour. In general, if the thickness of silicone raw material and the spacing of insection are constant, higher the sterilizing temperature, shorter the retention time. When the thickness of silicone raw material or the spacing of insection is larger, a higher sterilization temperature and/or a longer retention time is necessary.

Successful sterilization can be checked, for example, as follows:

A suitable biological indicator (herein after called BI. In the case of a high-pressure steam sterilizing, 10^6 *Bacillus stearothermophilus* is usually used as BI) is put on the center of silicone raw material sheet, then sealed leaving no opening, and the material is sterilized by a high-pressure steam sterilization, and dried. The BI is then taken out and incubated under an appropriate condition to check negative results. In the case of BI of *Bacillus stearothermophilus* is used, the result is checked after incubating in a soybean casein digestive (SCD) medium at 55°C to 60°C for seven days.

Step 2: Production of silicone preparations

Sterile silicone preparation is produced by mixing the silicone raw material sterilized as shown in Step 1, a sterilized powder containing an active ingredient, and optionally a sterilized powder of additives, etc, shaping the mixture, and curing the same.

The powder containing a sterilized active ingredient may be a powder comprising only an active ingredient, or a mixed powder containing an active ingredient and additive(s), or may be a

homogeneous solid containing an active ingredient and additive(s). In the case of a homogeneous solid containing the active ingredient and additive(s), for example, the sterilized powder containing an active ingredient can be produced by preparing a homogeneous solution of an active ingredient and additive(s), sterile filtering, and drying the solution to obtain a solid, followed by optionally powdering the solid and/or sieving. In this case, the drying can be done in conventional methods including as representatives flow drying using nitrogen, helium or air, vacuum drying, air drying, granulation, spray drying using spray dryer, or the like or a combination of them. These procedures are carried out under a sterile condition using a sterilized appliance and apparatus. The powder comprising only an active ingredient and the additive(s) may be also produced by a method similar to above one. Others include a method in which the production is conducted under a sterile condition from the beginning, a method in which the material at first is powdered before subjected to sterilization under dry heat or radiation, etc.

A silicone preparation having a single layer structure can be produced by mixing homogeneously a sterile silicone raw material, a sterile powder containing an active ingredient, and optionally a sterile powder of additive(s) with a kneader, a two-roll mill, etc., extruding the mixture through a nozzle to give a shape, and curing the same at 10°C to 200°C, which temperature depends on stability or property of the active agent and additive(s). All of the procedures are carried out under a sterile condition.

In the case of multi-layered silicone preparations, each layer

can be produced separately or at the same time. For example, when a single-centered cylindrical type preparation is produced, the following methods can be used, but are not restrictive: a method in which an inner layer in a stick form is prepared, then coated with a solution of an outer layer substance, and the material is dried; a method in which an inner layer produced separately is inserted into a tube prepared from an outer layer substance; a method in which an inner layer is shaped within a tube prepared from an outer layer substance; a method in which an inner layer and an outer layer are extruded at the same time using a nozzle to give a shape. The stick composition thus prepared may be cut in an appropriate length to give a desired preparation.

Examples

For further description of the present invention, the following examples and test examples are presented, but they are not intended to limit the scope of the invention.

Example 1

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (containing a primary agent organopolysiloxane, a filler and a curing catalyst) (12.5 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 5 mm. Separately, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (12.5 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to about 2.5 mm. Onto the 2.5 mm sheet, a BI (*Bacillus stearothermophilus* 10^6, ATCC No. 7953, paper strip type, STS Co.) was placed, the sheet was folded to cohere silicone

and BI not leaving the opening to be exposed to the outside environment, thus its thickness being adjusted to 5 mm (This caused the BI to be located at the deepest position of the silicone sheet, where it is positioned at 2.5 mm in deep from the surface exposed to the outer environment). Each sample was enclosed in a Tetoron sheet, packed in a sterile bag separately, and placed in a high-pressure steam sterilization apparatus (Auto high- pressure steam sterilizer personal clave HA-300 MIIC, Hirayama). The apparatus was set at 121°C and 60 minutes, and the sterilization was carried out. After sterilizing, the samples were taken out and dried to obtain a sterilized silicone raw material, Component A-1. Similarly, SILA- STIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B (containing a primary agent organopolysiloxane, a filler, a crosslinking agent, and a curing inhibitor) was also sterilized to obtain a sterilized silicone raw material, Component B-1.

Experiment 1

From the sterilized silicone raw materials, Components A-1 and B-1 into which the BI were inserted, BI-1 and BI-2 were taken out. Untreated BI-3 was prepared for a reference. These BIs were incubated in SCD medium at 55°C - 60°C for seven days and assayed.

Result (n=2):

BI-1	negative
BI-2	negative
BI-3	positive

The results of this experiment revealed that BI bacteria enclosed in the silicone raw materials were killed, showing that the high-pressure steam sterilization can sterilize an inner part of the

silicone raw materials.

Example 2

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (25 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 10 mm. Separately, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (25 g) was shaped to a sheet, using a two-roll mill. A BI (*Bacillus stearothermophilus* 10^6, ATCC No. 7953, paper strip type, STS Co.) was positioned at the central part of the sheet to cohere silicone and BI not leaving the opening to be exposed to the outside environment, thus its thickness being adjusted 10 mm (This caused the BI to be located at the deepest position, where it is positioned at 5 mm in deep from the surface exposed to the outer environment). Each sample was enclosed in a Tetoron sheet, packed in a sterile bag separately, and placed in a high-pressure steam sterilization apparatus (Auto high-pressure steam sterilizer personal clave HA-300 MIIC, Hirayama). The apparatus was set at 121°C and 120 minutes, and the sterilization was carried out. After sterilizing, the samples were taken out and dried to obtain a sterilized silicone raw material, Component A-2. Similarly, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B was also sterilized to obtain a sterilized silicone raw material, Component B-2.

Experiment 2

From the sterilized silicone raw materials, Components A-2 and B-2, BI-4 and BI-5 were taken out. Untreated BI-6 was prepared for a reference. These BIs were incubated in SCD medium at 55°C - 60°C

for seven days and assayed.

Result (n=2):

BI-4	negative
BI-5	negative
BI-6	positive

The results of this experiment revealed that BI bacteria enclosed in the silicone raw materials were killed, showing that the high-pressure steam sterilization can sterilize an inner part of the silicone raw materials.

Example 3

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (12.5 g) was shaped to a sheet, using a two-roll mill so that the thickness was adjusted to 5 mm. Separately, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (12.5 g) was shaped to a sheet, using a two-roll mill. A BI (*Bacillus stearothermophilus* 10^5, ATCC No. 7953, paper strip type, STS Co.) was positioned at the central part of the sheet to cohere silicone and BI not leaving the opening to be exposed to the outside environment, thus its thickness being adjusted 5 mm (This caused the BI to be located at the deepest position of the silicone sheet, where it is positioned at 2.5 mm in deep from the surface exposed to the outer environment). Each sample was enclosed in a Tetoron sheet, packed in a sterile bag separately, and placed in a high-pressure steam sterilization apparatus (Auto high-pressure steam sterilizer personal clave HA-300 MIIC, Hirayama). The apparatus was set at 123°C and 40 minutes, and the sterilization was carried out. After sterilizing, the samples were taken out and dried to obtain a sterilized silicone raw

material, Component A-3. Similarly, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B was also sterilized to obtain a sterile silicone raw material, Component B-3.

Experiment 3

From the sterilized silicone raw materials, Components A-3 and B-3, BI-7 and BI-8 were taken out. Untreated BI-9 was prepared for a reference. These BIs were incubated in SCD medium at 55°C - 60°C for seven days and assayed.

Result (n=2):

BI-7	negative
BI-8	negative
BI-9	positive

The results of this experiment revealed that BI bacteria enclosed in the silicone raw materials were killed, showing that the high-pressure steam sterilization can sterilize an inner part of the silicone raw materials.

Example 4

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (12.5 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 5 mm. Separately, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (12.5 g) was shaped to a sheet, using a two-roll mill. A BI (*Bacillus stearothermophilus* 10^6, ATCC No. 7953, paper strip type, STS Co.) was positioned at the central part of the sheet to cohere silicone and BI not leaving the opening to be exposed to the outside environment, thus its thickness being adjusted 5 mm (This caused the BI to be located at the deepest position of the silicone sheet,

where it is positioned at 2.5 mm in deep from the surface exposed to the outer environment). Each sample was enclosed in a Tetoron sheet, packed in a sterile bag separately, and placed in a high-pressure steam sterilization apparatus (Auto high-pressure steam sterilizer personal claveHA-300 MIIC, Hirayama). The apparatus was set at 123°C and 60 minutes and the sterilization was carried out. After sterilizing, the samples were taken out and dried to obtain a sterilized silicone raw material, Component A-4. Similarly, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B was also sterilized to obtain a sterile silicone raw material, Component B-4.

Experiment 4

From the sterilized silicone raw materials, Components A-4 and B-4, BI-10 and BI-11 were taken out. Untreated BI-12 was prepared for a reference. These BIs were incubated in SCD medium at 55°C - 60°C for seven days and assayed.

Result (n=2 each):

BI-10	negative
BI-11	negative
BI-12	positive

The results of this experiment revealed that BI bacteria enclosed in the silicone raw materials were killed, showing that the high-pressure steam sterilization can sterilize an inner part of the silicone raw materials.

Example 5

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (10 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 10 mm. This is enclosed in

a Tetoron sheet, packed in a sterile bag, and placed in a high- pressure steam sterilization apparatus (Auto high-pressure steam sterilizer personal clave HA-300 MIIC, Hirayama). The apparatus was set at 121°C and 240 minutes, and the sterilization was carried out. After sterilizing, the samples were taken out and dried to obtain a silicone raw material, Component A-5. Similarly, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B was also sterilized to obtain a sterilized silicone raw material, Component B-5.

Experiment 5

The sterilized silicone raw material, Component A-5 (1 g) and the sterilized silicone raw material, Component B-5 (1 g) were mixed and the mixture was extruded through a nozzle of 0.5 mm diameter. Separately, non-sterilized silicone raw materials, Component A (1 g) and Component B (1 g) were mixed and the mixture was extruded through a nozzle of 0.5 mm diameter. These extruded rods of the products were allowed to stand for five days at 25°C to cure. The cured rods were cut to give pieces having a length of 5 cm. Tensile test was conducted on the pieces (EZ-test, Shimadzu) to determine their tensile stress (stress at 300% extension).

Result (n=4 each):

sample	M_{300} (mN/mm^2)
sterilized silicone	2841 ± 50
untreated silicone	2189 ± 118

The results of this experiment revealed that the silicone raw materials sterilized according to this invention could be cured similarly to a non-sterilized silicone raw material.

Example 6

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (5 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 5 mm. This is enclosed in a Tetoron sheet, packed in a sterile bag, and placed in a high- pressure steam sterilization apparatus (Auto high-pressure steam sterilizer personal clave HA-300 MIIC, Hirayama). The apparatus was set at 123°C and 80 minutes, and the sterilization was carried out. After sterilizing, the samples were taken out and dried to obtain a sterilized silicone raw material, Component A-6. Similarly, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B was also sterilized to obtain a sterile silicone raw material, Component B-6.

Experiment 6

The sterilized silicone raw material, Component A-6 (1 g) and the sterilized silicone raw material, Component B-6 (1 g) were mixed and the mixture was extruded through a nozzle of 0.5 mm diameter. Separately non- sterilized silicone raw materials, Component A (1 g) and Component B (1 g) were mixed and the mixture was extruded through a nozzle of 0.5 mm diameter. These extruded rods of the products were allowed to stand for five days at 25°C to cure. The cured rods were cut to give pieces having a length of 5 cm and tensile test was conducted on the pieces (EZ-test, Shimadzu) to determine their tensile stress (stress at 300% extension).

Result (n=4 each):

sample	M_{300} (mN/mm^2)
sterilized silicone	3058 ± 28
untreated silicone	2395 ± 47

The results of this experiment, revealed that the silicone raw

materials sterilized by the high-pressure steam sterilization could be cured similarly to a non-sterilized silicone raw material.

Example 7

Human serum albumin powder (0.6 g) was dissolved in an aqueous solution of interferon (100 MU/mL, 347 mL) and the solution was sterile filtered using a 0.22 μm filter, and lyophilized under a sterile condition. The following procedures were all carried out using sterile appliances under a sterilized environment. The lyophilized cake was powdered to give Powder 1. Sterilized silicone raw material, Component A-1 (0.35 g) and sterilized silicone raw material, Component B-1 (0.35 g) were mixed together. Immediately after the mixing, Powder 1 (0.3 g) was kneaded within the mixture. The kneaded material was extruded through a nozzle of diameter 2 mm by pressure and was allowed to stand for three days at 25°C to cure. The product was cut to give a sterile silicone preparation.

Example 8

Sterilized silicone raw material, Component A-1 (0.35 g) and sterilized silicone raw material, Component B-1 (0.35 g) were mixed together. Immediately after the mixing, powder 1 (0.3 g) is kneaded with the mixture. Separately, sterilized silicone raw material, Component A-1 (50 g) and sterilized silicone raw material, Component B-1 (50 g) were mixed together. Through a nozzle of diameter 2 mm arranged to give an inner layer from the mixture comprising powder 1 and sterilized silicone raw materials, and to give an outer layer from sterilized silicone raw materials, the materials were extruded by pressure, and were allowed to stand for three days at 25°C to cure.

The product was cut to give a sterile silicone preparation.

Reference Example 1

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (40 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 10 mm. Each sample was packed in a sterile bag, and irradiated with gamma ray of 15 kGy, 25 kGy or 50 kGy; or electron beam of 20 kGy, 40 kGy or 60 kGy, (each n = 2) to obtain Reference silicone raw materials, Components A-1, A-2, A-3, A-4, A-5, and A-6.

Experiment 7

Properties of Reference silicone raw materials, A-1 to A-6, and of untreated silicone raw material were compared. The samples (0.25 g each) were mixed with 5 ml of toluene and the mixtures were stirred overnight. The solubility of samples was compared.

Result:

Sample	Property	Solubility
Reference silicone raw material, Component A-1	cured	insoluble
Reference silicone raw material, Component A-2	cured	insoluble
Reference silicone raw material, Component A-3	cured	insoluble
Reference silicone raw material, Component A-4	cured	insoluble
Reference silicone raw material, Component A-5	cured	insoluble
Reference silicone raw material, Component A-6	cured	insoluble
Untreated silicone raw material, Component A	no curing	soluble

These results show that even at under lower amount of irradiation, the silicone raw materials are cured, and therefore the

irradiation sterilization is not capable of being used to sterilize silicone raw materials.

Reference Example 2

SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component A (10 g) was shaped to a sheet using a two-roll mill so that the thickness was adjusted to 5 mm. Each sample was heated at 180°C for one hour or 135°C for five hours to obtain Reference silicone raw materials, Components A-7 and A-8. In a similar manner, SILASTIC (registered trade mark) medical grade ETR elastomer Q7-4750, Component B (10 g) was heated to obtain Reference silicone raw materials, Components B-1 and B-2.

Experiment 8

Reference silicone raw materials, Components A-7 and A-8, Reference silicone raw materials, Components B-1 and B-2, and untreated silicone raw materials, Components A and B were masticated using a two-roll mill. Usually, mastication with a two-roll mill improves plasticity. However, when the silicone raw materials are deteriorated, the masticated materials lose their plasticity and become brittle. The characters of each sample after mastication were compared.

Result:

Sample	Property
Reference silicone raw material, Component A-7	plastic
Reference silicone raw material, Component A-8	plastic
Untreated silicone raw material, Component A	plastic
Reference silicone raw material, Component B-1	scorch*

Reference silicone raw material, Component B-2	scorch*
Untreated silicone raw material, Component B	plastic

*) The term "scorch" is referred to as a state where a curing develops to some extent that a process for shaping a material cannot be done.

The above results show that a dry-heat sterilization under a usual condition such as one at 180°C for one hour or one at 135°C for five hours causes silicone raw materials, especially Component B, to be deteriorated, and thus such methods are not applicable to the sterilization.

Industrial applicability

The present invention provides a sterile silicone raw material. The invention enables to produce a sterile silicone preparation containing any active ingredient, irrespective of stability of the active ingredient that would be affected under various sterilization conditions.

CLAIMS

1. A process for sterilizing a silicone raw material for producing a silicone preparation, which comprises conducting a high-pressure steam sterilization on the silicone raw material prior to curing.

2. The process of claim 1, wherein the sterilization is conducted at about 115°C to about 135°C in a high-pressure steam sterilization apparatus.

3. The process of claim 1, wherein the silicone raw material is of an addition-polymerizable type by catalytic action of a platinum compound.

4. The silicone raw material sterilized by the process of claim 1 or 2.

5. A silicone preparation containing an active ingredient, which preparation is produced from a silicone raw material sterilized by the process of claim 1 or 2.

6. A process for producing a silicone preparation, which comprises sterilizing a silicone raw material for producing the silicone preparation prior to curing by a high-pressure steam sterilization.

INTERNATIONAL SEARCH REPORT

tional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L2/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 556 828 A (MENICON CO LTD) 25 August 1993 (1993-08-25) claims; examples	1-6
A	US 4 465 487 A (NAKAMURA HIDEKI ET AL) 14 August 1984 (1984-08-14) claims	1-6
A	EP 0 980 892 A (NISSHO KK) 23 February 2000 (2000-02-23) claims	1-6

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2001	09/10/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

	tional Application No PCT/JP 01/04203

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT.

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